

(12) UK Patent Application (19) GB (11) 2 283 745 (13) A

(43) Date of A Publication 17.05.1995

(21) Application No 9422158.7

(22) Date of Filing 03.11.1994

(30) Priority Data

(31) 152620

(32) 12.11.1993

(33) US

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(74) continued overleaf

(51) INT CL⁶

C07D 209/26, A61K 31/405

(52) UK CL (Edition N)

C2C CAA CLZ CMA CMC CMM CQS CQT CUH C1343
C213 C22Y C220 C25Y C250 C251 C30Y C31Y C311
C313 C314 C315 C32Y C323 C324 C326 C332 C337
C338 C35X C351 C355 C36Y C364 C366 C367 C37Y
C373 C387 C389 C396 C397 C464 C490 C613 C614
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C697 C698 C712 C80Y C802
U1S S2416 S2417

(56) Documents Cited

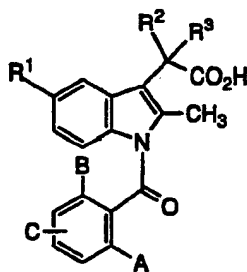
Chemical Abstracts 106:50037 and JP610148160 A2

(58) Field of Search

UK CL (Edition M) C2C CUH
INT CL⁵ C07D 209/26
Online databases: CAS ONLINE

(54) Pharmaceutically active N-acylindoles

(57) Compounds of the structure shown below and pharmaceutically acceptable salts thereof are specific inhibitors of cyclooxygenase-2 useful in the treatment of cyclooxygenase-2 mediated disease states such as inflammation, pain and fever, and are non-ulcerogenic:



R¹ is -OCH₃, -N(CH₃)₂, -SCH₃, -OCF₃, halo or lower alkyl;

R² and R³ are independently H or lower alkyl or R² and R³ may be joined to form a saturated hydrocarbon ring of 3 to 7 members;

A is halogen, lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, CF₃, CN, N₃, NO₂, SCF₃ or OCF₃;

B is A or also H if A is CF₃;

C is A or H with the proviso that if A is CF₃, B and C are not both H;

GB 2 283 745 A

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TITLE OF THE INVENTION

N-ACYLINDOLES AND RELATED COMPOUNDS

BACKGROUND OF THE INVENTION

5 This invention relates to novel N-acylindoles and related compounds; to methods of treating cyclooxygenase mediated diseases with the novel compounds; and to certain pharmaceutical compositions therefor.

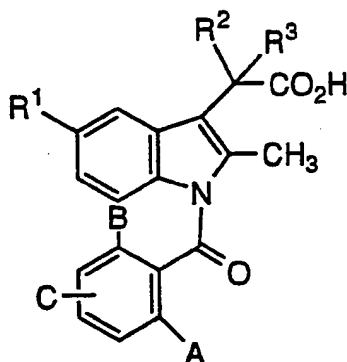
10 Non-steroidal, antiinflammatory drugs exert most of their antiinflammatory, analgesic and antipyretic activity and inhibit hormone-induced uterine contractions and certain types of cancer growth through inhibition of prostaglandin G/H synthase, also known as cyclooxygenase. Initially, only one form of cyclooxygenase was known, this corresponding to cyclooxygenase-1 (COX-1) or the constitutive
15 enzyme, as originally identified in bovine seminal vesicles. More recently the gene for a second inducible form of cyclooxygenase (cyclooxygenase-2) (COX-2) has been cloned, sequenced and characterized initially from chicken, murine and human sources. This enzyme is distinct from the cyclooxygenase-1 which has been cloned,
20 sequenced and characterized from various sources including the sheep, the mouse and man. The second form of cyclooxygenase, cyclooxygenase-2, is rapidly and readily inducible by a number of agents including mitogens, endotoxin, hormones, cytokines and growth factors. As prostaglandins have both physiological and pathological
25 roles, we have concluded that the constitutive enzyme, cyclooxygenase-1, is responsible, in large part, for endogenous basal release of prostaglandins and hence is important in their physiological functions such as the maintenance of gastrointestinal integrity and renal blood flow. In contrast, we have concluded that the inducible form,
30 cyclooxygenase-2, is mainly responsible for the pathological effects of prostaglandins where rapid induction of the enzyme would occur in response to such agents as inflammatory agents, hormones, growth factors, and cytokines. Thus, a selective inhibitor of cyclooxygenase-2 will have similar antiinflammatory, antipyretic and analgesic properties

to a conventional non-steroidal antiinflammatory drug, and in addition would inhibit hormone-induced uterine contractions, have potential anti-cancer effects and be useful in the treatment of Alzheimer's disease, but will have a diminished ability to induce some of the mechanism-based side effects. In particular, such a compound should have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and possibly a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects.

U.S. Patents 3,161,654, 3,647,858 and 3,654,349 disclose compounds similar to those of the present invention. It has now been unexpectedly found that compounds with a substituent A in structure I fixed in the ortho position of the phenyl group attached to Y exhibit marked selectivity for the inhibition of Cox-2 over Cox-1.

SUMMARY OF THE INVENTION

This invention relates to the novel compound of Formula I.

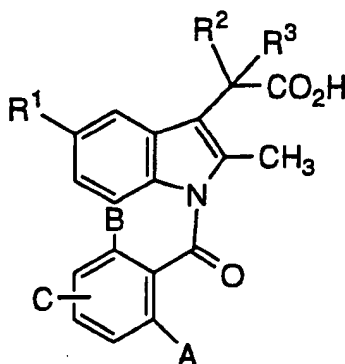


I

The invention also relates to certain pharmaceutical compositions for treatment of cyclooxygenase-2 mediated diseases comprising compounds of Formula I; to a method of treating cyclooxygenase-2 mediated diseases comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I; and to process for the preparation of the novel compounds of Formula I.

DETAILED DESCRIPTION OF THE INVENTION

The novel compound of this invention is represented by structural Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

R¹ is -OCH₃, -N(CH₃)₂, -SCH₃, OCF₃, halo, or lower alkyl;

R² and R³ are independently H or lower alkyl or R² and R³ may be joined to form a saturated hydrocarbon ring of 3 to 7 members;

A is halogen, lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, CF₃, CN, N₃, NO₂, SCF₃ or OCF₃;

B is A or also H if A is CF₃;

C is A or H with the proviso that if A is CF₃, B and C are not both H;

For purposes of the present specification the following terms have the indicated meanings.

"Lower alkyl" means alkyl groups of from 1 to 7 carbon atoms of a straight, branched or cyclic configuration. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, s- and t-butyl, pentyl, hexyl, heptyl, cyclopropyl, cyclobutylmethyl, cycloheptyl, and the like.

"Lower alkoxy" means alkoxy groups of from 1 to 7 carbon atoms of a straight, branched, or cyclic configuration.

Examples of lower alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy, and the like.

5 "Lower alkylthio" means alkylthio groups of from 1 to 7 carbon atoms of a straight, branched or cyclic configuration. Examples of lower alkylthio groups include methylthio, propylthio, isopropylthio, cycloheptylthio, and the like. By way of illustration, the propylthio group signifies $\text{-SCH}_2\text{CH}_2\text{CH}_3$.

10 "Lower alkylsulfinyl" means those alkylsulfinyl groups of from 1 to 7 carbon atoms of straight, branched or cyclic configuration. Examples of lower alkylsulfinyl groups are methylsulfinyl, 2-butylsulfinyl, cyclohexylmethylsulfinyl, and the like. By way of illustration the 2-butylsulfinyl group signifies $\text{-S(O)CH(CH}_3\text{)CH}_2\text{CH}_3$.

15 "Lower alkylsulfonyl" means those alkylsulfonyl groups of from 1 to 7 carbon atoms of a straight, branched or cyclic configuration. Examples of lower alkylsulfonyl groups are methylsulfonyl, 2-butylsulfonyl, cyclohexylmethylsulfonyl, and the like. By way of illustration the 2-butylsulfonyl group signifies $\text{-S(O)}_2\text{CH(CH}_3\text{)CH}_2\text{CH}_3$.

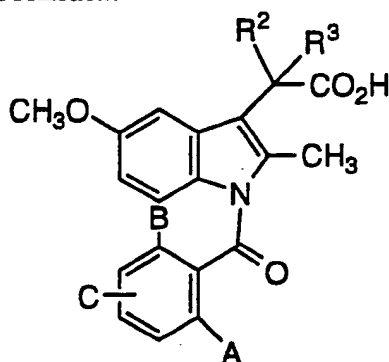
20 Halogen includes F, Cl, Br, and I.

Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers and mixtures thereof as well as their racemic and resolved, enantiomerically pure forms and other mixtures of the enantiomers and pharmaceutically acceptable salts thereof.

25 The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, 30 lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including

naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine,
5 N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

10 One embodiment of the novel compounds of this invention is that with structural formula:



20 Specific compounds representative of this embodiment are those depicted in Table I.

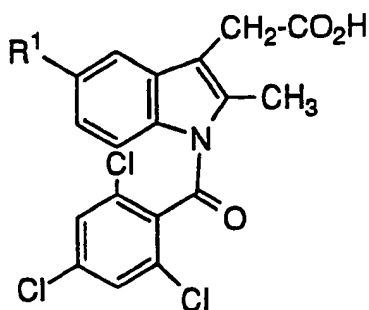
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Table I

	A	B	C	R ²	R ³
5	Cl	Cl	4-Cl	H	H
	Cl	Cl	4-Cl	CH ₃	H
	Cl	Cl	H	H	H
	CF ₃	H	4-CF ₃	H	H
10	CF ₃	CF ₃	H	H	H
	F	F	H	H	H
	Cl	F	H	H	H
	Br	Cl	H	CH ₃	H
15	Br	Cl	4-Cl	H	H
	CF ₃	Cl	4-Cl	CH ₃	CH ₃
	OCH ₃	OCH ₃	H	H	H
	Cl	Cl	4-S(O) ₂ CH ₃	H	H
20	Cl	Cl	4-SCH ₃	H	H
	Cl	Cl	4-S(O)CH ₃	H	H
	CH ₃	CH ₃	H	H	H
	CH ₃	Cl	4-Cl	H	H
25	NO ₂	Cl	H	H	H
	SCH ₃	Cl	4-Cl	H	H
	CN	Cl	H	H	H
	I	Cl	H	H	H
30	N ₃	Cl	H	H	H
	SCF ₃	Cl	4-Cl	H	H
	OCF ₃	Cl	H	H	H
	S(O) ₂ CH ₃	Cl	4-Br	H	H

Another embodiment of the novel compounds of the present invention is the compound of the following structure:



Specific compounds representative of this structure are indicated in Table II.

Table II

R¹
F
Cl
CH(CH₃)₂
N(CH₃)₂
S-CH₃
OCF₃

It will be understood that in the discussions of pharmaceutical compositions and methods of treatment which follow, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Another embodiment of this invention comprises the method of treatment using the Compound of Formula I for the relief of pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, injuries, and following surgical and dental procedures. In addition, the

novel compound may inhibit cellular neoplastic transformations and metastatic tumor growth and hence can be used in the treatment of cancer. Compound 1 may also be of use in the treatment and/or prevention of cyclooxygenase-mediated proliferative disorders such as may occur in diabetic retinopathy and tumour angiogenesis.

Compound I will also inhibit prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence may be of use in the treatment of dysmenorrhea, premature labor and asthma.

By virtue of its high cyclooxygenase-2 (COX-2) activity and/or its specificity for cyclooxygenase-2 over cyclooxygenase-1 (COX-1), compound I will prove useful as an alternative to conventional non-steroidal antiinflammatory drugs (NSAID'S) particularly where such non-steroidal antiinflammatory drugs may be contra-indicated such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; GI bleeding, coagulation disorders including anemia such as hypoprothrombinemia, haemophilia or other bleeding problems; kidney disease; those prior to surgery or taking anticoagulants.

A fourth embodiment of this invention includes pharmaceutical compositions comprising the compound of Formula I as active ingredient. For the treatment of any of these cyclooxygenase mediated diseases compound I may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle sheep, dogs, cats, etc., the compound of the invention is effective in the treatment of humans.

In further aspects, the invention encompasses pharmaceutical compositions for treating cyclooxygenase-2 mediated diseases as defined above comprising a non-toxic therapeutically

effective amount of the compound of Formula I as defined above and one or more ingredients such as another pain reliever including acetaminophen or phenacetin; a potentiator including caffeine; an H₂-antagonist, aluminum or magnesium hydroxide, simethicone, a
5 decongestant including phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine; an antiitussive including codeine, hydrocodone, caramiphen, carbetapentane, or dexamethorphan; a diuretic; a sedating or
10 non-sedating antihistamine. In addition the invention encompasses a method of treating cyclooxygenase mediated diseases comprising: administration to a patient in need of such treatment a non-toxic therapeutically effect amount of the compound of Formula I, optionally co-administered with one or more of such ingredients as listed
15 immediately above.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible
20 powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring
25 agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium
30 phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the

gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Patent 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax,

hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

5 Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already
10 mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for
15 example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation
20 products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and
25 flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also
30 be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or

suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

5 Compound I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

10 For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula I are employed. For purposes of this application, topical application shall include mouth washes and gargles.

15 Dosage levels of the order of from about 0.01 mg to about 140 mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5 mg to about 7 g per patient per day. For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day, or alternatively about
20 0.5 mg to about 3.5 g per patient per day.

 The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral
25 administration of humans may contain from 0.5 mg to 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient, typically 25
30 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

 It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of

administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

5 In the process discussions and the Examples that follow, the following abbreviations have the indicated meanings:

	DMAP	=	4-(dimethylamino)pyridine
	HMPA	=	hexamethyl phosphoric triamide
10	KHMDS	=	potassium hexamethyldisilazane
	NSAID	=	non-steroidal anti-inflammatory drug
	r.t.	=	room temperature
	rac.	=	racemic
	THF	=	tetrahydrofuran
15	TLC	=	thin layer chromatography
	C ₃ H ₅	=	allyl
	Me	=	methyl
	Et	=	ethyl
	n-Pr	=	normal propyl
20	i-Pr	=	isopropyl
	n-Bu	=	normal butyl
	i-Bu	=	isobutyl
	s-Bu	=	secondary butyl
	t-Bu	=	tertiary butyl
25	c-Pr	=	cyclopropyl
	c-Bu	=	cyclobutyl
	c-Pen	=	cyclopentyl
	c-Hex	=	cyclohexyl

30 The compounds of the present invention can be prepared according to the following methods.

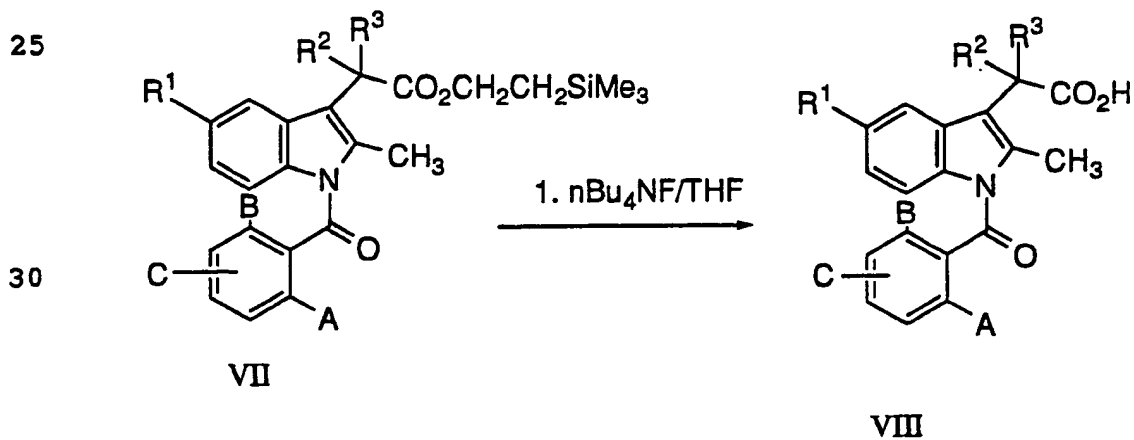
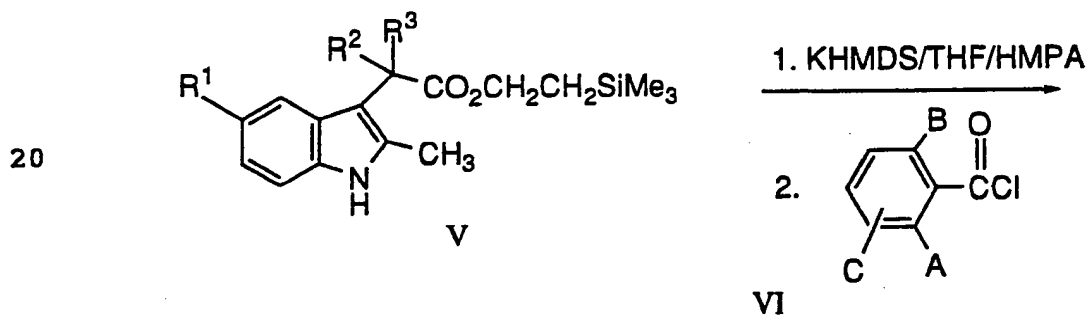
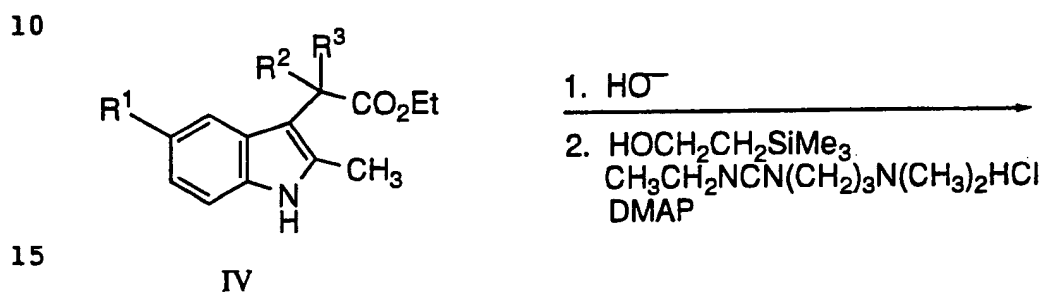
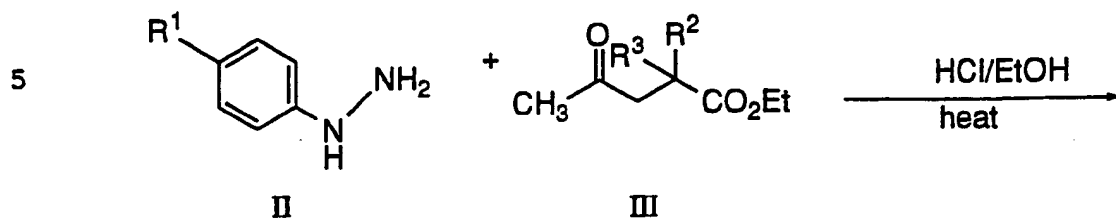
Method A

The indolyl compounds (IV) are easily prepared from the condensation of substituted phenylhydrazines II with substituted levulinic ethyl esters III, as described in a U.S. Patent # 3,161,654. After hydrolysis of the ester and esterification with 2-trimethylsilyl-ethanol in the presence of 1-(3-Dimethylaminopropyl)-3-ethyl-carbodiimide•HCl and DMAP, the ester derivatives V are obtained. The acylation of the nitrogen can be achieved by deprotonation of the nitrogen with KHMDS in THF/HMPA followed by the addition of an appropriate benzoyl chloride VI to afford VII. The 2-(trimethylsilyl)ethyl ester group can be then removed by fluoride treatment (TBAF).

Method B

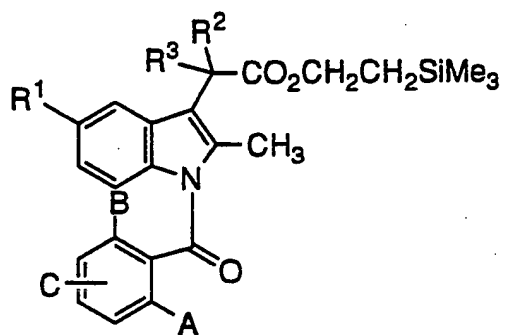
The formation of a saturated ring (X) may be accomplished from VII when $R^2=R^3=H$ by deprotonation and bis-alkylation with a dihalogenated alkyl (Dox et al., J. Am. Chem. Soc. 1921, p. 2097 and Stewart et al., J. Org. Chem. 1965, p. 1451.

Method A

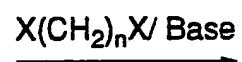


Method B

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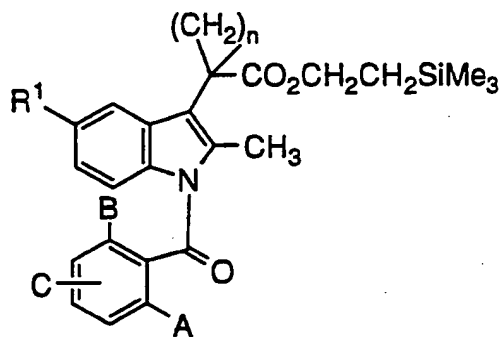


10



VII $R^2, R^3 = H$

15

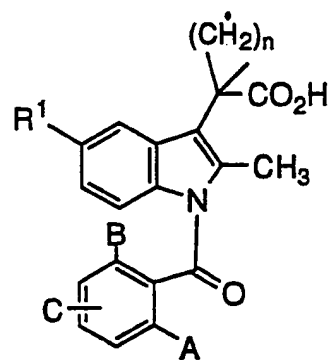


20



IX

25



30

X

$n = 2-6$

The compound of Formula I can be tested using the following assays to determine their cyclooxygenase-2 inhibiting activity.

Inhibition of Cyclooxygenase Activity

5

Compounds were tested as inhibitors of cyclooxygenase activity in whole cell and microsomal cyclooxygenase assays. Both of these assays measured prostaglandin E₂ synthesis in response to arachidonic acid, using a radioimmunoassay. Cells used for whole cell
10 assays, and from which microsomes were prepared for microsomal assays, were human osteosarcoma 143 cells (which specifically express cyclooxygenase-2) and human U-937 cells (which specifically express cyclooxygenase-1). In these assays, 100% activity is defined as the difference between prostaglandin E₂ synthesis in the absence and
15 presence of arachidonate addition.

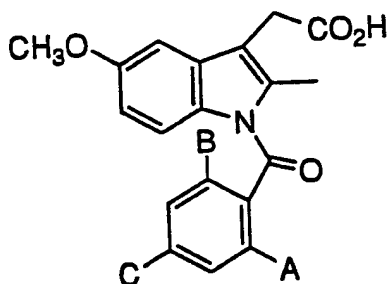
Rat Paw Edema Assay - Protocol

Male Sprague-Dawley rats (150-200 g) were fasted
20 overnight and were given po either vehicle (1% methocel) or a test compound. One hr later, a line was drawn using a permanent marker at the level above the ankle in one hind paw to define the area of the paw to be monitored. The paw volume (V_0) was measured using a plethysmometer (Ugo-Basile, Italy) based on the principle of water
25 displacement. The animals were then injected subplantarily with 50 μ l of 1% carrageenan solution in saline (FMC Corp, Maine) into the paw using an insulin syringe with a 25-gauge needle (i.e. 500 μ g carrageenan per paw). Three hr later, the paw volume (V_3) was measured and the increases in paw volume ($V_3 - V_0$) were calculated. The animals were
30 sacrificed by CO₂ asphyxiation and the absence or presence of stomach lesions scored. Data were compared with the vehicle-control values and percent inhibition calculated. Since a maximum of 60-70% inhibition (paw edema) was obtained with standard NSAIDs, ED₃₀ values were

used for comparison. All treatment groups were coded to eliminate observer bias.

Compounds of the present invention are inhibitors of cyclooxygenase-2 and are thereby useful in the treatment of cyclooxygenase-2 mediated diseases as enumerated above. The activities of the compounds against cyclooxygenase may be seen in the representative results shown below. In the assay, inhibition is determined by measuring the amount of prostaglandin E₂ (PGE₂) synthesized in the presence of arachidonic acid, cyclooxygenase-1 or cyclooxygenase-2 and a putative inhibitor. The IC₅₀ values represent the concentration of putative inhibitor required to return PGE₂ synthesis to 50% of that obtained as compared to the uninhibited control.

The results for inhibition of PGE₂ production may be seen in Table III.



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			IC ₅₀ (μM)	
			Whole cell	
A	B	C	COX-1	COX-2
Cl	Cl	Cl	>100	1.0
Cl	Cl	H	>100	10.0

The invention is illustrated by the following non-limiting examples in which, unless stated otherwise:

- 5 (i) all operations were carried out at room or ambient temperature, that is, at a temperature in the range 18-25°C,
- (ii) evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 10 4.5-30 mm. Hg) with a bath temperature of up to 60°C.,
- (iii) the course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only;
- 15 (iv) melting points are uncorrected and 'd' indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations;
- 20 (v) the structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data;
- 25 (vi) yields are given for illustration only;
- 30 (vii) when given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300 MHz or 400 MHz using the indicated solvent; conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc.: in addition "Ar" signifies an aromatic signal;

(viii) chemical symbols have their usual meanings; the following abbreviations have also been used v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).

EXAMPLE 1

1-(2,4,6-Trichlorobenzoyl)-5-methoxy-2-methyl-3-indolyl acetic acid

Step 1: 5-Methoxy-2-methyl-3-indolyl acetic acid 2-(trimethylsilyl)ethyl ester

To a mixture of 5-methoxy-2-methyl-3-indolyl acetic acid (8.9 g, Aldrich) and 2-trimethylsilylethanol (7.0 mL) in dichloromethane (100 mL) at 0°C was added DMAP (500 mg) followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (8.56 g) portionwise. After stirring overnight at room temperature, the reaction mixture was diluted with CH₂Cl₂ and washed with water (x2) and dried. The organic layer was evaporated to dryness and the residue was crystallized from EtOAc/hexane to give 9.3 g of the titled compound. Further reprocessing of the mother liquor afforded a further 2.0 g of the material to give a total of 11.3 g.

¹H NMR (acetone - d₆) δ 0.02 (9H, s), 0.98 (2H, m), 2.38 (3H, s), 3.62 (2H, s), 3.78 (3H, s), 4.13 (2H, m), 6.66 (1H, dd), 6.97 (1H, d), 7.15 (1H, d), 9.70 (1H, bs).

Step 2: 1-(2,4,6-Trichlorobenzoyl)-5-methoxy-2-methyl-3-indolyl acetic acid 2-(trimethylsilyl)ethyl ester

To 5-methoxy-2-methyl-3-indolyl acetic acid 2-(trimethylsilyl)ethyl ester (2.00 g) in THF (20.0 mL) was added HMPA (2.0 mL). To the resulting mixture at -78°C was added a 0.5M toluene solution of KHMDS (13.8 mL). After a period of 0.5 h, 2,4,6-trichlorobenzoyl chloride (1.03 mL) was added and the mixture was stirred 0.5 h at

-78°C then 0.5 h at 0°C. An aqueous solution of NH₄Cl was then added and extracted with EtOAc. After purification by flash chromatography (10% EtOAc in hexane) the title compound was obtained (2.80 g) and used as such for the next step.

Step 3: 1-(2,4,6-Trichlorobenzoyl)-5-methoxy-2-methyl-3-indolyl
acetic acid

To 1-(2,4,6-trichlorobenzoyl)-5-methoxy-2-methyl-3-indolyl acetic acid 2-(trimethylsilyl)ethyl ester (2.80 g) in THF (25.0 mL) at 0°C was added TBAF (14.7 mL). After a period of 5 h at room temperature, the reaction mixture was acidified by the addition of NH₄Cl and HCl, extracted with EtOAc, dried over Na₂SO₄ and evaporated. The resulting solid was washed with 10% EtOAc in hexane and recrystallized (EtOAc-hexane) to afford 1.73 g of the title compound, m.p. 193-196°C.

The following Examples were prepared according to the above-described methods.

EXAMPLE 2

1-(2,6-dichlorobenzoyl)-5-methoxy-2-methyl-3-indolyl acetic acid

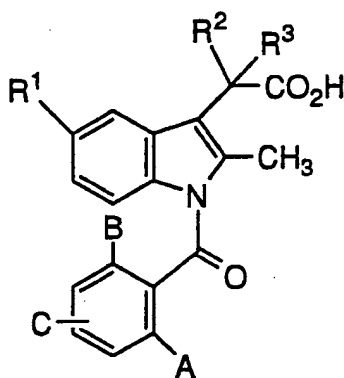
¹H NMR (400 MHz) CD₃COCD₃ mixture of rotamers in the ratio of 1.81.

Major rotamer δ 1.86 (3H, s), 3.70 (2H, s), 3.88 (3H, s), 6.97 (1H, m), 7.14 (1H, m), 7.65 (3H, m), 8.47 (1H, d).

Major rotamer δ 2.75 (3H, s), 3.77 (2H, s), 3.79 (3H, s), 5.96 (1H, d), 6.56 (1H, d), 7.15 (1H, m), 7.65 (3H, m).

WHAT IS CLAIMED IS:

1. A compound of structural formula:



I

or a pharmaceutically acceptable salt thereof, wherein:

R¹ is -OCH₃, -N(CH₃)₂, -SCH₃, -OCF₃, halo or lower alkyl;

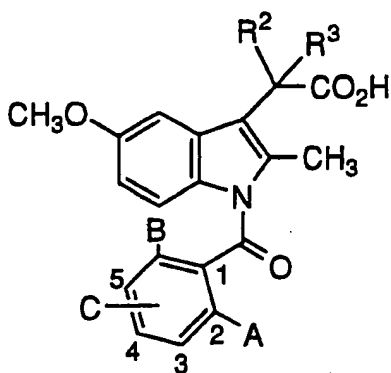
R² and R³ are independently H or lower alkyl or R² and R³ may be joined to form a saturated hydrocarbon ring of 3 to 7 members;

A is halogen, lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, CF₃, CN, N₃, NO₂, SCF₃ or OCF₃;

B is A or also H if A is CF₃;

C is A or H with the proviso that if A is CF₃, B and C are not both H;

2. The compound of Claim 1 of structural formula:

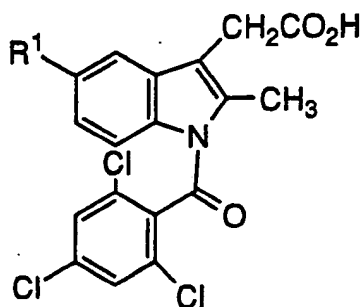


3. The compound of Claim 2 selected from the group consisting of those depicted in the following table:

Table I

	A	B	C	R ²	R ³
5	Cl	Cl	4-Cl	H	H
	Cl	Cl	4-Cl	CH ₃	H
	Cl	Cl	H	H	H
	CF ₃	H	4-CF ₃	H	H
10	CF ₃	CF ₃	H	H	H
	F	F	H	H	H
	Cl	F	H	H	H
	Br	Cl	H	CH ₃	H
15	Br	Cl	4-Cl	H	H
	CF ₃	Cl	4-Cl	CH ₃	CH ₃
	OCH ₃	OCH ₃	H	H	H
	Cl	Cl	4-S(O) ₂ CH ₃	H	H
20	Cl	Cl	4-SCH ₃	H	H
	Cl	Cl	4-S(O)CH ₃	H	H
	CH ₃	CH ₃	H	H	H
	CH ₃	Cl	4-Cl	H	H
25	NO ₂	Cl	H	H	H
	SCH ₃	Cl	4-Cl	H	H
	CN	Cl	H	H	H
	I	Cl	H	H	H
30	N ₃	Cl	H	H	H
	SCF ₃	Cl	4-Cl	H	H
	OCF ₃	Cl	H	H	H
	S(O) ₂ CH ₃	Cl	4-Br	H	H

4. The compound of claim 3 with structural formula:



5. The compound of Claim 4 selected from the group consisting of these wherein R¹ is -F, -Cl, -CH(CH₃)₂, -N(CH₃)₂, -SCH₃ or -OCF₃.

6. A pharmaceutical formulation comprising a pharmaceutically acceptable carrier and an effective cyclooxygenase-2 inhibitory amount of the compound of Claim 1.

7. A method of inhibiting cyclooxygenase-2 in a patient in need of such treatment which comprises the administration of an effective amount of the compound of Claim 1.

Relevant Technical Fields

- (i) UK Cl (Ed.M) C2C (CUH)
(ii) Int Cl (Ed.5) C07D 209/26

Databases (see below)

(i) UK Patent Office collections of GB, EP, WO and US patent specifications.

(ii) ONLINE DATABASES: CAS ONLINE

Search Examiner
MR P DAVEY

Date of completion of Search
8 DECEMBER 1994

Documents considered relevant
following a search in respect of
Claims :-
1-7

Categories of documents

- | | |
|--|---|
| <p>X: Document indicating lack of novelty or of inventive step.</p> <p>Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.</p> <p>A: Document indicating technological background and/or state of the art.</p> | <p>P: Document published on or after the declared priority date but before the filing date of the present application.</p> <p>E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.</p> <p>&: Member of the same patent family; corresponding document.</p> |
|--|---|

Category	Identity of document and relevant passages	Relevant to claim(s)
X	Chemical Abstracts 106:50037 and JP 610148160 A2 (GREENCROSS CORP) see abstract	1,2,6,7

Databases: The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).